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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/214,645	09/27/1999	JAY M. SHORT	09010/046001	8386

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LISA A. HAILE PH.D.
GRAY CARY WARE & FREIDENRICH LLP
4365 EXECUTIVE DRIVE
SUITE 1600
SAN DIEGO, CA 92121

EXAMINER
SISSON, BRADLEY L

ART UNIT	PAPER NUMBER
1634	22

DATE MAILED: 02/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/214,645	SHORT, JAY M.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 September 1999* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *18* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 21 November 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/214,645 is acceptable and a CPA has been established. An action on the CPA follows.

Drawings

2. New formal drawings are required in this application because of the objections identified on the PTO-948 attached to Paper No. 7. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 2, and 4-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The Quantity of Experimentation Necessary

The quantity of experimentation is on the order of several man-years with little if any reasonable expectation of success. It is noted with particularity that it is a requirement that one mutate the nucleic acid from any source such that any desired property of an encoded polypeptide can be realized. This is most problematic, not only in relation to the specific mutagenic agents specifically identified, but to the innumerable other agents encompassed by the claims yet not identified. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of nucleic acids, and by extension, the proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative embodiments. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which can be tolerated in a protein's amino acid sequence and still retain similar biological activity requires a (1) knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which re conserved (*i.e.*, expectantly intolerant to modification), and (2) detailed knowledge of the ways in which the protein's structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in

turn utilizing predicted structural determination to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the real of routine experimentation.

One of the main considerations to be made in determining whether undue experimentation is required is the amount of experimentation required. See *In re Wands*, 8 USPQ2d 1400 (CAFC 1988). Even if substitutions with the natural 20 amino acids encoded by DNA were the only modifications, a limitation that the present claims explicitly exceed, the instant claims would still broadly encompass a multitude of species; calculated as 20^N * (length)!/N/(length-N)! wherein "20" is the number of natural amino acids encoded by DNA, "N" is the number of positions where substitutions can occur, "!" is the factorial symbol, "/" is the division symbol and "length" is the total number of amino acids in the protein or peptide. In putting these numbers in perspective, it is noted that the earth is estimated to have existed for 10^{17} seconds (see Creighton, T.E. 1983. Proteins: Structure and Molecular Principles, W. H. Freeman and Company, NY. 93-94, page 94, paragraph 1). There are an estimated 10^{79} atoms in the universe (see page 231 of Creighton, Prog. Bophys. Molec. Biol. 33:231-233, 1975). A polypeptide chain of 100 amino acids could exist in 10^{130} combinations and "just one molecule of each of these different proteins would fill the entire [known] universe 10^{27} times over, even if packed together in the most efficient manner" (see paragraph 1, page 94 of 1983 Creighton reference).

While recombinant and mutagenic techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable

expectation of success in obtaining similar biological activity are limited in any protein. The result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g., multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acid modifications in such proteins.

The specification does not support the broad scope of the claims that encompass all modifications and fragments because the specification does not disclose the following:

a) The amino acid sequence for all proteins nor the nucleotide sequence tht encodes said proteins;

b) The general tolerance to modification and extent of such tolerance;

c) The specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical;

d) What fragments, if any, can be made which retain the biological activity of any intact protein, regardless of source; and

f) The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance so to enable one of skill in the art to make and use the modified proteins in a manner reasonably correlated with the scope of the claims, broadly including any number of additions, deletions, or substitutions and fragments of any size. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

" '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').

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"Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
"It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

The Amount of Direction or Guidance Provided

The amount of guidance is extremely limited.

The Presence or Absence of Working Examples

The specification provides but 4 prophetic examples:

- Example 1, page 64, Generation of Random Size Polynucleotides Using U.V. Induced Photoproducts.
- Example 2, pages 64, Isolation of Random Size Polynucleotides.
- Example 3, page 65, Shuffling of Isolated Random Size 100-300 bp Polynucleotides.
- Example 4, page 65, Screening of Polypeptides from Shuffled Polypeptides.

The Nature of the Invention

The claimed invention relates directly to matters of physiology and chemistry, which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

The State of the Prior Art

The area of art to which the invention belongs is undeveloped and quite unpredictable. To complicate matters, the claimed method does not involve any method steps that would screen for otherwise target the amplification interruption/mutagenizing means to a polypeptide having a desired property. Rather, the method seemingly has one to target entire cells or genomic libraries.

> Upon review of the specification it is seen that one does not target entire cells but rather works with isolated polynucleotides. Even using the prophetic examples for guidance leaves the skilled artisan wanting for further guidance to practice the claimed invention as the specification is essentially silent as to just how one intuitively selects for a polypeptide with a "desired property." The specification

is equally forthcoming is providing some guidance as to the probability of finding useful mutated polypeptides so as to establish some frame work within which one of skill in the art can gauge their relative success or lack thereof. While the specification dos provide many suggestions as to how the problems of the subject invention may be approached, it is essentially left up to the public to resolve the operational conditions so to fully enable the claimed invention. The situation at hand is analogous to that in *Genentech, supra.*

The Relative Skill of Those in the Art

The relative skill of those in the art that is most closely associated with the claimed invention is high, on par with those that hold a Ph.D. in biochemistry.

The Breadth of Scope of the Claims

The claims have sufficient breadth of scope to encompass the generation of any mutation in any and all possible coding sequences as found in any life form, and in any level of heterogeneity. The method also encompasses the generation of new coding sequences where there are none and the production of "useful" polypeptides of unknown properties. And perhaps most daunting of all, the claims encompass the modification of said any nucleic acid sequence so that any desired effect will be achieved, be it a cure for aging, cancer, AIDS, etc.

In view of the foregoing remarks, and in the absence of convincing evidence to the contrary, the specification has not been found to enable the claimed invention and as such, stand rejected under 35 USC 112, first paragraph, as not being enabled by the instant specification.

5. Acknowledgement is made of applicant's argument that the rejection of claims under 35 USC 112, first paragraph, should be withdrawn as "Applicants have provided a process for producing mutant polypeptides which express a useful mutant polypeptide by a series of steps" (response of 21 November 2001). This response has been fully considered and has not been

found persuasive. While applicant's argument recites the aspect of the encoded polypeptide being "useful," such is not a limitation of the claims. The rejection of all claims under 112, first paragraph, is maintained against previously pending claims and is expanded so to include newly added claims as applicant has not shown how a "desired property" can be routinely and reproducibly realized by the claimed method of mutagenesis where any one, combination of one or all, or even additional agents can be combined into a single method where a polypeptide having a desired property will result. It is not enough that applicant might be able to generate some polypeptides as the expressed, mutated polypeptides must also have the "desired property." Newly added claims recite a plethora of reagents that may be used in the method. Indeed, in keeping with claims 1 and 2, all of these reagents plus many more may be used simultaneously in the claimed method and the artisan still be able to achieve a nucleic acid sequence that encodes, and is used to express, any polypeptide that has any desired property. A most daunting feat for which there is inadequate guidance.

Claim Rejections - 35 USC § 101/112

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1 and 9 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible and substantial asserted utility or a well-established utility.

The method of claims 1 and 9 is directed to the generation of mutated polynucleotides in a recombinant cell system, which comprises the interruption or blocking of polynucleotide synthesis, by any number of possible routes. The claimed method places no limitation on the type or types of mutated polynucleotides nor is there any assurance that the mutated polynucleotide(s) are involved in the coding or regulation of any gene, much less a gene that has been found to be useful, and lesser still that the mutation will in and of its self result in any useful product

Claims 1 and 9 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to argument

9. At pages 6-7 of the response applicant presents argument that by claim 1 having been amended so to recite that the polypeptide has a "biological activity or desired property," the rejection should be removed. This argument ahs been fully considered and has not been found to be persuasive. Any and all nucleic acids have various "biological properties," one being that they can serve as a carbon source, yet such does not rise to the level of a substantial utility. While the method may also result in the generation of nucleic acid sequences that encode for a portion of a gene, such is equivalent to the generation of Expressed Sequence Tags or ESTs. For

while they may in fact encode something, just what it is and what it is useful for is anything but certain.

10. Applicant is urged to consider narrowing the claims to where they are directed to a method where the polypeptide has a "desired property."

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claims 2, 6-8 and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Pues et al.

13. Pues et al., disclose the generation of mutated nucleic acid sequences through a variation of inverse polymerase chain reaction (IPCR). The resultant mutated sequences are then introduced into a vector (in double stranded form) and expressed. Clones expressing a protein with the desired characteristic are selected.

Response to argument

14. Applicant presents argument that the reference is not available prior art as "[t]he publication date of Pues et al. is after Applicants' priority date of July 9, 1996, therefore Pues et al. is not even available as 'prior art.'"

15. Applicant's argument has been fully considered and has not been found to be persuasive. The subject application, US Serial No. 09/214,645, was filed on 27 September 1999 and is a

Rule 371 application of PCT/US97/12239, filed July 9, 1997. Applicant is requested to present evidence that shows applicant has a priority date of 1996.

Conclusion

16. This is a CPA of applicant's earlier Application No. 09/214,645. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

17. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

19. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

20. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

bls
February 9, 2002